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Histologic prognostic factors in ependymoma

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Abstract. The prognostic value of a series of histologic signs and clinical features was studied in a series of 298 ependymomas, collected from different institutions. The distribution of tumor sites varied in relation to patient age, with infratentorial cases prevailing under 4 years. Life table univariate analysis demonstrated as highly significant prognostic factors: (1) the number of mitoses; (2) endothelial hyperplasia; (3) necrosis; (4) intracranial site; (5) age <4 years. Multivariate analysis by tumor site revealed mitoses cell density, age >16 years in supratentorial cases, and subependymoma in infratentorial cases to be prognostically important. Comparison of the anaplastic variant with the other tumor types in intracranial cases did not show a significant difference in survival even though the median survival time of anaplastic cases was shorter. The main conclusion is that the histological criteria employed to diagnose anaplasia in gliomas are not useful for recognizing anaplasia in ependymomas. The number of mitoses is a very important prognostic factor in supratentorial cases, whereas endothelial proliferations and necroses are much less important as prognostic factors than in gliomas.

Key words: Ependymomas – Prognostic factors – Pediatric – Brain tumor – Ependymoblastoma

Ependymomas are tumors that occur infrequently, but when [3] they do they are relatively often located in the spine [6, 27]. The age distribution is broad [35], they frequently occur in childhood, they show four preferential locations, and they vary greatly from a histological point of view.

Many papers have reported the identification of histological variants, even though they seem to be devoid of any prognostic significance [25]. A malignant variant has been recognized, but its frequency varies greatly in different series [34].

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Contrasting results have been obtained with the application of various systems for grading malignancies [1, 2, 7, 10, 13, 15, 16] with either four or three grades. The malignant variant did not seem to be constantly and significantly associated with a poor prognosis [26, 30]. Also, the prognostic significance of histological factors is uncertain [8, 12, 23]. To identify prognostic factors with statistical significance, a large series of tumors must be studied. This report contains information on our study of the correlations and prognostic values of histologic and clinical features in our series of 298 ependymomas (108 of which were in children).

Materials and methods

Two hundred and ninety-eight cases, consecutively operated on between 1960 and 1988, were collected from different neurosurgical institutions (see list).

All cases were histologically studied and 220 patients (84 children) were sufficiently followed up. Thirty patients (9 children) died within 30 days of surgery (surgical death); thus 190 (75 children) were eligible for the analysis of prognostic factors.

All surgical specimens were fixed in 10% formalin or cold Carnoy and studied by the following histological methods: hematoxylin-eosin, Luxol fast blue B+PAS+hematoxylin, Gomori for reticulin, glial fibrillary acid protein, vimentin and factor VIII/RAg were stained immunohistochemically, according to the peroxidase-antiperoxidase method [33]. Thirty cases were also studied by electron microscopy: specimens were fixed in 2.5% glutaraldehyde, postfixed in osmium tetroxide, and embedded in Epon.

The following histological parameters were analyzed and categorized. The evaluation was the result of an agreement among three observers (DS, MTG, RS). In childhood tumors there is no peculiar histological aspect in comparison with adults.

1. Histological type: cellular, epithelial, anaplastic, with subependymomatous areas, myxopapillary, classic subependymoma, ependymoblastoma. There were only a few cases with papillary aspects and they were thus included in the other types. The anaplastic variant was diagnosed with generally acknowledged criteria: nuclear polymorphism, mitoses, circumscribed necroses, and endothelial hyperplasia.

2. Cell density: low, <400 cells × HPF (high-power field) (×400); medium, 400 to 800 cells × HPF; high, >800 cells × HPF. These figures refer to tumor regions with the highest cell number (Fig. 1a).

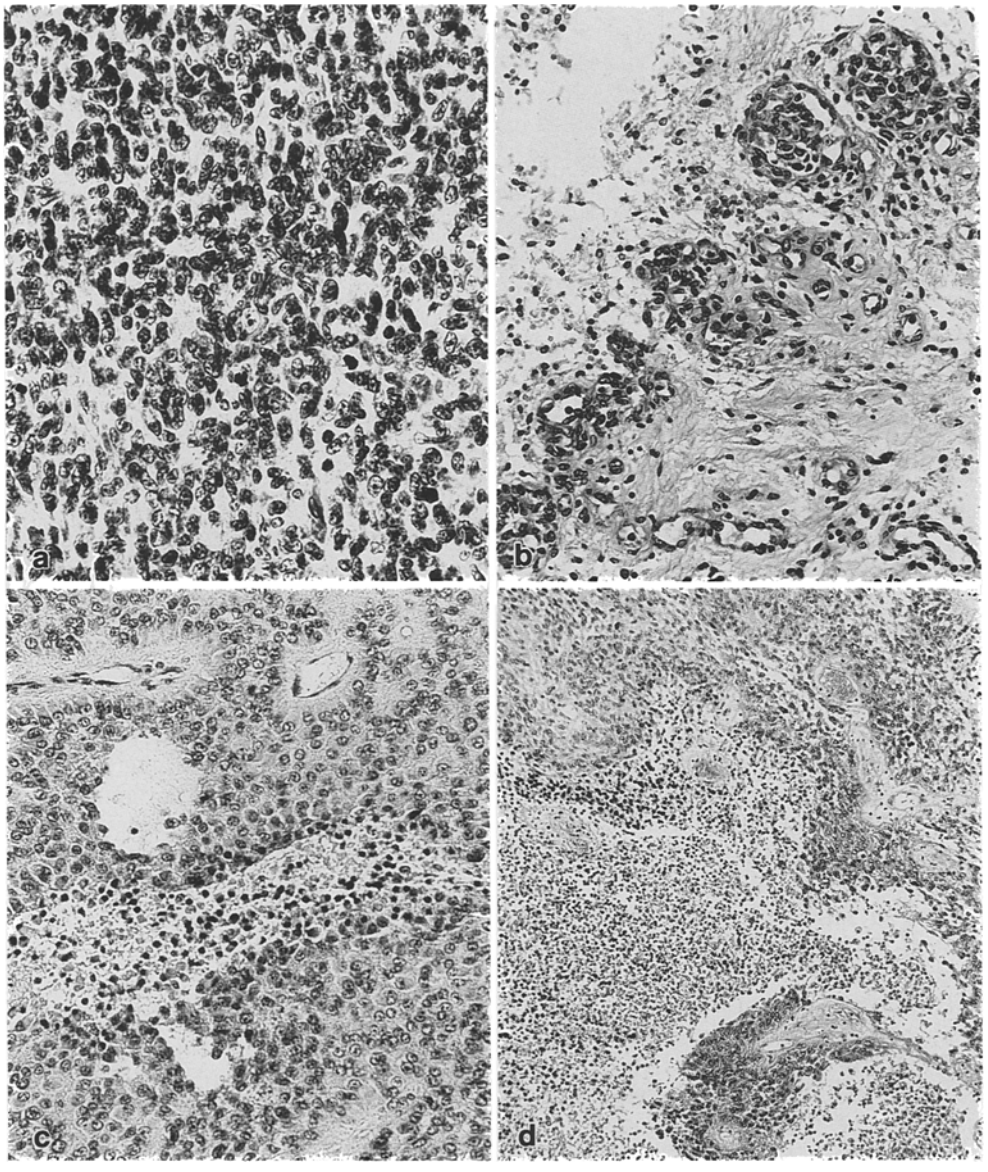

Fig. 1. **a** Very high cell density with many mitoses, H & E, ×40(**b** Wall of glomeruli, H & E, ×200. **c** Circumscribed necrosis, H & E, ×400. **d** Extensive necrosis, H & E, ×100

3. Nuclear polymorphism: absent, moderate, or high.

4. Nuclear inclusions: absent or present.

5. Mitoses × 10 HPF: 0=4.9; 5=19.9; >20 (Fig. 1a).

6. Perivascular round cell infiltrates: absent or present.

7. Microcysts: absent or present.

8. Vessel frequency: normal or increased (on a semiquantitative basis).

9. Vessel walls: normal or thickened.

10. Mesodermic areas (with or without mitoses): absent or present.

11. Endothelial hyperplasia: absent; incipient; intense.

12. Endothelial mitoses: absent or present.

13. Vessel glomeruli: absent or present (Fig. 1b).

14. Perivascular pseudorosettes: absent or present (with short or long processes, enlarged, deformed).

15. Non-perivascular pseudorosettes: absent or present.

16. Ependymal rosettes: absent or present (with mitoses, multilayered).

17. Canals: absent or present (single- or multilayered).

18. Pseudopapillae: absent or present.

19. Necroses: absent or present (circumscribed with or withou pseudopalisading, large, both types; Fig. 1c, d).

20. Rosenthal fibres: absent or present.

21. Calcifications: absent or present.

22. Astrocytic aspects (piloid or stellate): absent or present.

23. Clear cells: absent or present.

24. Subependymomatous areas: absent or present (with fibrous fiel or cell nests or both).

25. Nodular growth: absent or present.

26. Limits regarding normal nervous tissue: well demarcated or wit infiltration.

The regional variability of some parameters (cell density, nuclea polymorphism, number of mitoses, endothelial hyperplasia, necro sis) was recorded. The clinical factors taken into consideration were tumor site (supratentorial, infratentorial, spinal, conus-cauda-filur

Table 1. Distribution of ependymomas according to age groups and tumor site

	All cases, no. (%)	<4 years, no. (%)	4–16 years, no. (%)	>16 years, no. (%)
Supratentorial	72 (25)	13 (34)	23 (33)	36 (19)
Infratentorial	101 (34)	26 (66)	35 (51)	40 (21)
Spinal	35 (11)	–	6 (9)	29 (15)
Conus-cauda-filum	90 (30)	–	5 (7)	85 (45)
All sites	298	39	69	190

Table 2. Distribution of ependymomas according to tumor site and histological type. CCF, Conus-cauda-filum region

	Supra-tentorial, no. (%)	Infra-tentorial, no. (%)	Spinal, no. (%)	CCF, no. (%)
Cellular	40 (55)	64 (63)	33 (94)	43 (48)
Epithelial	7 (10)	7 (7)	–	9 (10)
With subependymomatous areas	1 (1)	14 (14)	–	–
Mixopapillary	–	–	–	38 (42)
Anaplastic	17 (24)	10 (10)	–	–
Ependymoblastoma	4 (6)	1 (1)	–	–
Subependymoma	3 (4)	5 (5)	2 (6)	–
All types	72	101	35	90

Table 3. Distribution of ependymomas according to age groups and histological type

	<4 years, no. (%)	4–16 years, no. (%)	>16 years, no. (%)
Cellular	15 (38)	47 (68)	118 (62)
Epithelial	2 (5)	6 (9)	15 (8)
With subependymomomatous areas	6 (15)	7 (10)	2 (1)
Myxopapillary	–	6 (9)	32 (17)
Anaplastic	11 (28)	3 (4)	13 (7)
Ependymoblastoma	3 (11)	–	2 (1)
Subependymoma	2 (5)	–	8 (4)
All types	39	69	190

Table 4. Significant prognostic factors by tumor site (univariate analysis)

Supratentorial	Mitoses ($P<0.05$) Necroses ($P<0.05$)
Infratentorial	Age <4 years ($P<0.01$) Subependymoma ($P<0.05$)[a]
Spinal	None
Conus-cauda-filum	None

[a] Positive prognostic factor

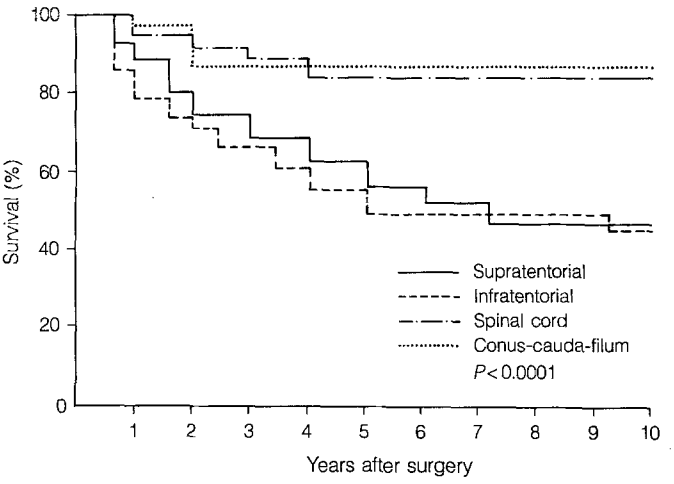

Fig. 2. Ependymomas (all cases): survival by tumor site

region), sex, and age (1–4 years, 5–16 years, over 16 years). No case under 1 year of age was available for survival analysis.

Survival was estimated by the Kaplan and Meier method [14]. Differences in survival were tested for statistical significance by the log-rank test [22]. Correlations among histological and clinical factors were studied using contingency tables. Statistical significance was evaluated using the chi-square test (assuming linear trend across categories for a variable with three or four levels). The Cox proportional hazard regression model [5] was used in a stepwise manner to determine the relative prognostic significance of individual factors.

Results

One hundred and forty-eight patients were male (52 children) and 150 female (56 children); 108 patients were children under 16 years, and 190 adults. The correlations between tumor site and age, tumor site and histological types, and age and histological types are reported in Tables 1–3.

The distribution of tumor sites varied in relation to patient age: infratentorial cases prevailed under 4 years, spinal and conus-cauda-filum sites increased in adults, and supratentorial ependymomas were more equally distributed. Of the histological types, the cellular one was the most frequent in all locations, the myxopapillary variant was limited to the conus-cauda-filum region, and the subependymoma prevailed in the infratentorial region, although it was also present in other regions. Tumors with subependymomatous areas prevailed in the posterior fossa, and the anaplastic type was exclusively made up of supra- and infratentorial locations. Ependymoblastoma was a typical supratentorial tumor.

The correlation between histological type and age showed that tumors with subependymomatous areas were typical of cases under 16 years, whereas the myxopapillary type was typical of adults. The anaplastic variant and the subependymoma were mostly represented in adults and children under four years of age.

Intracranial locations show a survival definitely shorter than spinal and conus-cauda-filum locations. Since site is thus a prognostic factor of paramount importance (Fig. 2), further life table analyses were carried out by sites.

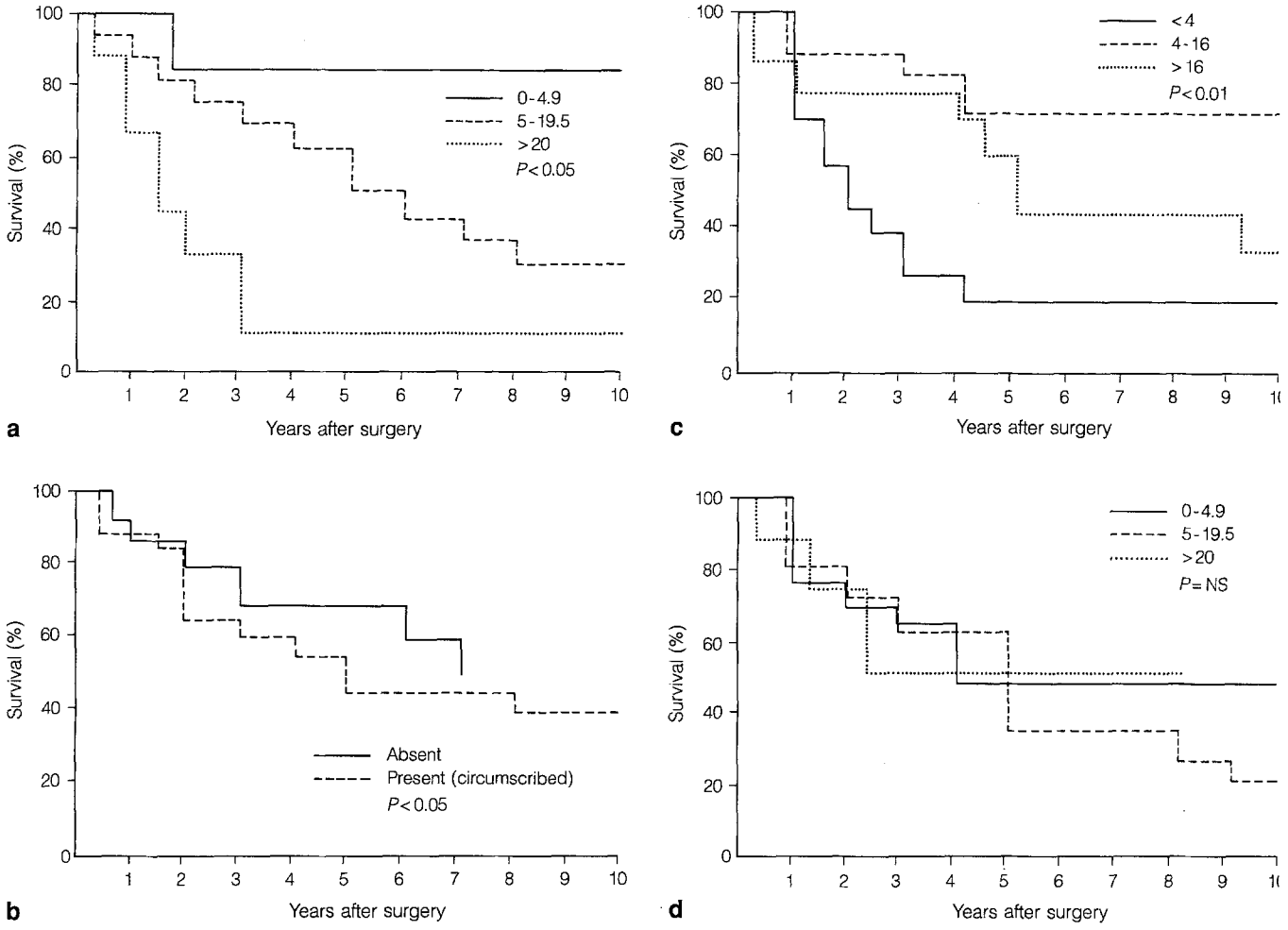

Fig. 3. Univariate analysis by tumor site: correlations between survival and mitoses (×10 HPF) in supratentorial cases (**a**), necroses in supratentorial cases (**b**), age in infratentorial cases (**c**), and mitoses (×10 HPF) in infratentorial cases (nonsignificant) (**d**)

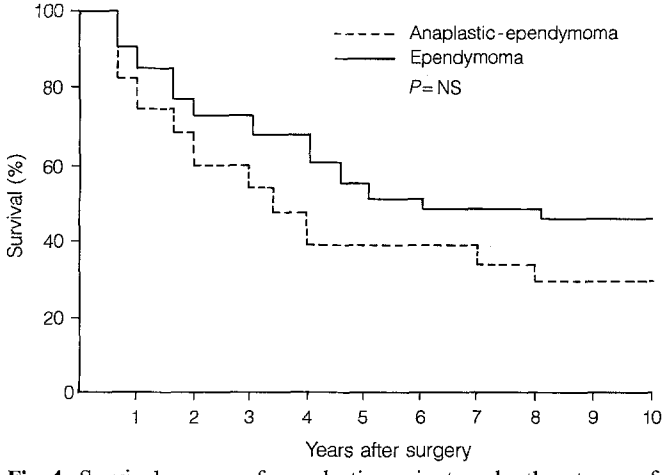

Fig. 4. Survival curves of anaplastic variant and other types of ependymoma

Life table univariate analysis by tumor site showed that the variables indicated in Table 4 were significant ($P<0.05$). In Fig. 3 the survival curves of significant variables are reported in addition to that for mitoses in infratentorial cases. Multivariate analysis by tumor site showed that the parameters indicated in Fig. 5 are prognostically relevant.

Table 5. Significant prognostic factors by tumor site (multivariate analysis)

Supratentorial	Mitoses ($P<0.0005$) Cell density ($P<0.005$) Age >16 years ($P<0.05$)
Infratentorial	Subependymoma ($P<0.05$)[a]
Spinal	None
Conus-cauda-filum	None

[a] Positive prognostic factor

If one only considers intracranial cases, the comparison of the anaplastic variant with non-anaplastic types showed no statistically significant difference in survival even though the median survival time of anaplastic cases was shorter (1201 days opposed to 2973 days) (Fig. 4). This may be due to the low number of anaplastic cases (Table 2). Separate evaluation of supratentorial and infratentorial tumors revealed no statistical significance even though the trend was a worse survival time for anaplastic cases.

Discussion

The distribution of our cases as to location and age corresponds to that described in the literature. In general, posterior fossa tumors are the most frequent, followed by those of the conus-cauda-filum region, which is consistent with the earlier observations of Mørk and Løken [18]. In children, infratentorial tumors are followed by supratentorial ones, whereas in adults tumors in the spinal and conus-cauda-filum region are largely represented [3, 18, 31].

The histological variants show no correlation with age or tumor site, with the exception of the myxopapillary variant, which is exclusive to the conus-cauda-filum region, and of the anaplastic variant, which is found exceptionally in spinal and conus-cauda-filum cases. Cases with subependymomatous areas more clearly prevailed in the posterior fossa and in childhood than classic subependymomas. Our data on the distribution of classic subependymomas correspond to those of Scheithauer [29].

Ependymoma is generally considered a semibenign tumor with a different frequency of the malignant variant in the numerous series [34]. Malignant ependymoma is recognized by the occurrence of nuclear polymorphism, high cell density, necroses, endothelial proliferations, and mitoses, as in gliomas [11, 24]. It has even been considered an ependymal glioblastoma [11], similar to the ependymal spongioblastoma of Globus and Kuhlenbeck [9]. In a highly malignant tumor, however, it is fundamental in order to recognize the tumor nature that at least some areas retain histological features typical of ependymoma [28]. The anaplastic ependymoma, recognized by the same criteria used for gliomas, showed contrasting correlations with prognosis [4, 18]. It seems, therefore, that recognition of the malignant variant is neither easy nor objective: in fact in six out of nine series examined, the percentage of highly malignant tumors varied from 40% to 94% [34].

The effort to recognize the malignant variant by DNA determination with microdensitometric techniques [19] and with flow cytometry [17, 32] has led to inconclusive results. The labeling index for BUdR has been reported to be high in three out of eight tumors: all three were clinically aggressive, but only one was histologically malignant [20].

A multivariate analysis on 102 cases [12] demonstrated a prognostic value for tumor site and age but not for mitoses; for posterior fossa tumors, the prognosis was better in adults than in children; subependymal areas and rosettes had a positive direct or inverse correlation with survival, respectively. In another series [23], in contrast, the only factor correlating with a good prognosis was the occurrence of microcysts in supratentorial tumors. There was no difference in survival between anaplastic and non-anaplastic tumors at 2 years or 3 years. No correlation between histological malignancy, evaluated on the basis of conventional signs, or survival has recently been found in a series of 15 cases of malignant ependymoma [26]. In a large series of 360 cases [8] it has been found that histologically benign posterior fossa tumors have a poor prognosis.

Histological signs associated with a bad prognosis would be hypervascularity, endothelial hyperplasia, mitoses, calcifications, and low cell density; on the other hand, histological signs associated with a good prognosis would be astrocytic areas, high cell density, and irregular nuclei. Of paramount importance is the observation that traditional histological subdivisions are of no prognostic value [25]. Excluding the large number of cases in the spinal and conus-cauda-filum region, which are well-known to have a long survival time, and analyzing the prognostic factors by tumor site, the individual factors by univariate analysis that correlated with a poor survival were the number of mitoses and necroses for supratentorial tumors, whereas in the posterior fossa an age of more than 4 years and subependymomas correlated with a better prognosis. The importance of a younger age in determining a poor prognosis in infratentorial tumors of childhood has also been reported by others [21].

Multivariate analysis of supratentorial cases confirmed the significance of the number of mitoses and reduced that of necroses. In infratentorial cases it did not prove any of the parameters if subependymomas were excluded. The number of mitoses in supratentorial tumors correlated with survival: cases with more than 20 mitoses $\times$ 10 HPF indicated a worse outcome.

The anaplastic variant in intracranial cases showed a trend towards a worse survival, but the difference with classic ependymomas was not statistically significant. This is consistent with the observation of Ross and Rubinstein [26].

In spite of the high number of cases our study does not solve the problem of the malignant variant. The difficulty of identifying the anaplastic variant with a prognostic significance may be due to several reasons. The regional variability of some histological features, such as cell density, necroses, mitoses, nuclear polymorphism, and endothelial hyperplasia, may be important. As a consequence, it appears very difficult to apply a grading system to ependymomas. Another reason may be the different significance of the same histological signs in astrocytic gliomas and ependymomas. For example, cell density is very difficult to quantify in ependymomas, even though some small or large foci of high cell density can be identified. Endothelial proliferation and glomeruli formation follow different mechanisms than in gliomas: glomeruli may arise from the confluence of many adjacent vessels, not from proliferation of endothelial buds. A trial to overcome the difficulty of categorizing malignancy has been conducted [21], establishing three pathological categories of infratentorial tumors in children on the basis of mitoses, necroses, and cell density. A correlation with survival was found. Our categorization of histological parameters in a series of intracranial ependymomas in adults and children is consistent with the above-mentioned results, but our figures on quantity of mitoses and distribution of necroses are different.

In conclusion, a malignant ependymoma is difficult to recognize histologically. In supratentorial tumors the number of mitoses and, to a lesser extent, cell density seem to be very important.

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